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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|--------------|------------------------|-----------------------|------------------|
| 09/754,826 | 01/04/2001 | Mohamed E. El Halawani | 600.492US1 | 3468 |
| 21186 | 7590 | 06/06/2002 | | |
| SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A. P.O. BOX 2938 MINNEAPOLIS, MN 55402 | | | EXAMINER | |
| | | | BELYAVSKYI, MICHAIL A | |
| ART UNIT | PAPER NUMBER | | | |
| 1644 | | | | |
| DATE MAILED: 06/06/2002 | | | | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 09/754,826 | EL HALAWANI ET AL. |
| | Examiner | Art Unit |
| | Michail A Belyavskyi | 1644 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM
 THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 19 April 2002.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-28 is/are pending in the application.
- 4a) Of the above claim(s) 9-28 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-8 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's election with traverse of Group I (Claims 1-8) in Paper No. 12, filed on 4/19/02 is acknowledged.

The traversal is on the ground(s) that the invention of Group I , that is myostatin immunoconjugate, is related to the claims directed to the use of that immunoconjugate and that there is no serious burden to search and examine the entire application.

This is not found persuasive because of the inventions must be independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed (see MPEP 806.05-806.05(I))) for the reasons of record set forth in the previous Office Action (Paper No.11). Regarding applicant's comments about undue burden, the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the examiner by the examination Groups I and II-V. The Inventions are distinct for reasons elaborated in paragraphs 4-6 of the previous Office Action.

The requirement is still deemed proper and is therefore made FINAL.

Claims 9-28 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 1-8 are under consideration in the instant application.

2. The instant application is in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.
3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.
4. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

5. The formal drawings submitted 10/16/01 have been approved by the Draftsperson.
6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.
7. The following is a quotation of the first paragraph of 35 U.S.C. □ 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. This is a rejection under 35 U.S.C. § 112, first paragraph, "written description" (and not a new matter)

Claims 1, 5-8 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

Claim 1 and dependent claims 5-8 recites myostatin immunoconjugate comprising a full length myostatin. The claim as written encompasses a broad genus of myostatin with unlimited number of possibilities with regard to the sources of myostatin. On page 18, line 14-19 of the current specification, it is noted that myostatin gene from only a number of vertebrate species can be employed to in the practice of the invention. These is insufficient written description encompassing "full length myostatin", because the relevant identifying characteristics such as sequences, structure and/or other physical and chemical characteristics are not set forth in the specification as filed, commensurate in scope with the claimed invention, as they read on non-vertebrate species.

In the absence of structural characteristics that are shared by members of the genus of "myostatin" one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Therefore, only vertebrate myostatin but not full breadth of the claimed myostatin, meets the written description provision of 35USC 112, first paragraph.

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Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is separable from its enablement provision. (See page 1115.)

9. Claims 1, 5-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "vertebrate myostatin, disclosed on page 18, line 14-19 of the instant specification, does not reasonably provide enablement for any "full length myostatin". The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has not provided sufficient biochemical information (e.g. sequences, molecular weight, amino acid composition, etc.) that distinctly identifies the "full length myostatin" "other than those encompassed by the disclosure of the vertebrate myostatin, disclosed on page 18 (line 14-19) of the instant specification.

While "full length myostatin" may have some notion of the similarity with a vertebrate myostatin, disclosed on page 18 (line 14-19) of the instant specification, claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make and use myostatin immunoconjugate, comprising full length myostatin.

Applicant is relying upon certain disclosed or asserted biological activities of an entire genus of "full length myostatin". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands. For example, it is noted that "full length myostatin" differ in structure and physicochemical properties.

"It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. full length myostatin) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of myostatin and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 (CCPA, 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

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Because of the lack of sufficient guidance and predictability in determining which structures would lead "full length myostatin", with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of myostatin immunoconjugate comprising a full length myostatin polypeptide.

Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance upon the certain "vertebrate myostatin", disclosed as filed does not appear to provide sufficient enabling support for "full length myostatin" encompassed by the claimed invention and so the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Without sufficient guidance, the changes which can be made in the structure of full length myostatin and still provide or maintain sufficient or the claimed activity of vertebrate myostatin is unpredictable and the experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claim1-4, 6-8 rejected under 35 U.S.C. 102(e) as being anticipated by Barker et al.(US. Pat. No. 6,369,201, see entire document).

Barker et al. teach full length myostatin polypeptide and myostatin immunoconjugate comprising at least one myostatin polypeptide, linked to an immunological carrier (Column 4, especially lines 1-4; column 7 lines 15-22, column 9, lines 22-35). In Detailed Description, Barker et al. teach that the term "myostatin immunogen" includes polypeptide of myostatin molecule, which elicits an immunological response (see column 6, lines14-25, column 15 lines 1-5, and column 16, lines 42-45).

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Barker et al. also teach vaccine composition comprising the myostatin polypeptide and pharmaceutically acceptable excipient (Column 4, line 10-15). In Detailed Description, Barker et al. teach that myostatin molecule is administrated in the mix with a pharmaceutically acceptable excipient, such as water, saline, dextrose , glycerol, ethanol. (Column 23, lines 45-65).

Barker et al. also teach that to enhance immunogenicity of myostatin, myostatin immunoconjugate which comprises a fusion polypeptide can be used. (see Detailed Description, Column 10, lines 5-10).

Barker et al. also teach myostatin that is derived from various species, including turkey myostatin. In column 4, line 55, Barker et al. teach turkey myostatin (SEQ ID No: 35) that comprises SEQ ID No:2 of the instant claim 3.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced myostatin immunoconjugate including immune composition thereof.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9 Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barker et al.(US. Pat. No. 6,369,201) in view of Harris et al. (Micron 1999, 30, 597-623).

Claims 1-8 are drawn to myostatin immunoconjugate, comprising myostatin polypeptide linked to a carrier.

Claim 5 recites that a carrier is keyhole limpet hemocyanin (KLH).

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The teaching of Barker et al. was discussed above. Berker et al. further teach that immunological carrier can be any molecule which, when associated with a myostatin immunogen, enhances the immunogenicity of the molecule. (Column 9, lines 22-34). Barker et al. do not explicitly teach that the carrier is KLH.

However, Harris et al. teach the widespread use of KLH as a hapten carrier and generalized vaccine component that is widely used to enhances the immunogenicity of the vaccine (see Abstract and entire document).

Given the teaching of Harris et al. that KLH is widely used as a carrier to enhance the immunogenicity of the vaccine, one of ordinary skill in the art would have find it obvious to modify the teaching of Barker et al. and substitute carrier described by Barker et al. for KLH carrier to enhances the immunogenicity of myostatin immunoconjugate. One of ordinary skill in the art at the time the invention was made would be motivated to substitute immunological carrier, described by Barker et al. for KLH carrier to enhances the immunogenicity of myostatin immunoconjugate. Finally, given the art recognize widespread use of KLH as a carrier to enhance the immunogenicity, one ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to generate a myostatin immunoconjugate, comprising a myostatin polypeptide linked to KLH as a carrier.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
May 30, 2002

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6/5/02